FDA Briefing Document

Cardiovascular and Renal Drugs Advisory Committee Meeting

September 10, 2014

To discuss the potential clinical utility of fixed-combination prescription drugs composed of an anti-hypertensive drug, aspirin, and a statin administered to reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with a history of cardiovascular disease.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this topic to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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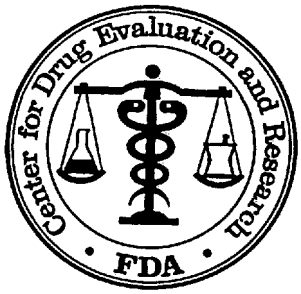

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Memo to Advisory Committee

The Agency has approved numerous two- and a few three-drug antihypertensive fixed-combination drugs based solely on the demonstration that each component drug contributes to the effect on blood pressure. Aspirin plus pravastatin and atorvastatin plus amlodipine are approved for patients for whom treatment with both component drugs is appropriate. The approvals of aspirin plus pravastatin and atorvastatin plus amlodipine were based on demonstration that neither component drug interfered with the other, either pharmacokinetically or pharmacodynamically. Although all of these drugs carry cardiovascular outcomes claims, no study was sought to establish the preservation of the outcome benefits when they were administered together.

The Agency initially required sponsors of combination anti-hypertensive drugs to develop, and then approved, all of the reasonable dose combinations, seeking to prevent the combination product from inhibiting titration of each component drug. It should be noted, however, the Agency could not require the manufacturer to market all the approved doses, and some doses disappeared. Over the last decade, the Agency has actively discouraged antihypertensive monotherapy and combination doses with effects that were very close together, considering them a nuisance to physicians seeking to get patients to goal.

The proposal to market a fixed-combination drug composed of aspirin, a statin, and one or more anti-hypertensive drug (which has been termed the “polypill”), all of which have cardiovascular claims, extends this discussion. While optimal care may require titrating the dose of some of the proposed component drugs to treatment goal, titration requires regular fruitful interaction with a learned intermediary. We believe there are patients in the USA for whom cardiovascular prevention therapy is appropriate but who cannot get the follow-up necessary for titration, for reasons that include geography, finances, and patient preference. While it is possible that a manufacturer may decide to market multiple doses of a polypill with various doses of the component drugs, what has been discussed in scientific literature has been fixed-dose combinations not intended to be titrated. We are asking then whether people who are not, for whatever reason, going to receive regular follow-up are better off on some reasonable doses of drugs for secondary prevention of cardiovascular disease, rather than none, even if they are not getting what is believed to be optimal care.

Points to Consider

1. Is there an appropriate target population for fixed-dose, untitratable combination drugs to reduce cardiovascular risk? Do you think you need to see data establishing benefit in this setting, i.e. is some type of outcome study required?

2. Is it likely that such therapy would be attractive only to the population for which it is intended? What are the public health consequences of the use of such a product in patients who could be getting care in an "optimal" setting? Do you think that you need to see data bounding this risk? What, if anything, needs to be done to mitigate this risk?

3. If such a product were submitted for marketing approval, what do you think they need to show, beyond components' potential for pharmacokinetic and pharmacodynamics interaction?

BACKGROUND DOCUMENT

for

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

on 10-September-2014

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August 14, 2014

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1. BACKGROUND INFORMATION ON THE POLYPILL

This background information on the Polypill is provided to the Cardiovascular and Renal Drugs Advisory Committee as reference for their discussion of

(i) the potential clinical utility of fixed-combination (FDC) prescription drugs composed of a one or more anti-hypertensive drugs, aspirin, and a statin administered to reduce the risk of cardiovascular (CV) death, nonfatal myocardial infarction (MI), and nonfatal stroke in patients with a history of cardiovascular disease (CVD),

(ii) the patient population that could benefit from such FDC products,

(iii) whether that population would be likely to take the FDC drug long term and how this could be assured, and

(iv) the advantages and disadvantages of a treatment that will not be titrated and in a setting where monitoring may not be rigorous.

From a historical perspective, Dr. Salim Yusuf[1,2] proposed in 2002 that use of a four-drug combination consisting of aspirin, a β-blocker, a statin and an ACE inhibitor for secondary prevention would result in a 75% reduction in patients' cumulative risk of CVD events. In 2003, Wald and Law[3] proposed that a six-drug combination 'Polypill' {which contained three antihypertensive drugs at half maximal doses (thiazide, ACE inhibitor, and β-blocker), aspirin, a statin and folic acid} could potentially reduce ischemic heart disease events by 88% and stroke by 80%, and recommended that this Polypill be taken by all individuals who had a CVD event and by anyone >55 years, without reference to their CV risk or monitoring treatment to attain specific targets. The objective of the Polypill was to improve simultaneously four key CV risk factors: low density lipoprotein cholesterol (LDL-C), blood pressure (BP), serum homocysteine levels, and platelet function. Wald and Law contended that sub-maximal doses of multiple antihypertensive drugs can significantly lower BP with fewer side effects than the full dose and can reduce the risk of IHD by 46% and stroke by 63%.

Various sponsors have had discussions with FDA about developing fixed-combination drugs with various components such as aspirin, statins, and antihypertensive drugs for approval to be marketed in the USA. In general, the doses of component statins and anti-hypertensive drugs in the proposed polypills were not the maximum available doses. Further the drugs were being developed with one or two doses of the component drugs (i.e. not containing all of the possible dose combinations) and the doses of the component statins and anti-hypertensives were not meant to be titrated as was recommended in the contemporary US professional guidelines. FDA initially expressed skepticism that the convenience of having a pill with submaximal doses of drugs proven to reduce mortality and serious morbidity is adequate justification for potential under treatment. FDA's view evolved in response to the following:

- The realization that there are patients in the United States for whom cardiovascular prevention therapy is appropriate but who are unlikely to get the follow-up necessary for titration, for reasons that include geography, finances, and patient preference.
- The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults found insufficient evidence to recommend titrating statin doses to

attain specific LDL-cholesterol levels

- Several literature reports indicating titrating a single anti-hypertensive drug to the maximally recommended dose is likely less desirable both in terms of the magnitude of BP reduction and as tolerability than administering more than one anti-hypertensive drug at submaximal doses.

FDA now feels it appropriate to ask the committee for advice as to the appropriate development pathway for a polypill, intended to be marketed in the USA, for prevention of CV death, MI and stroke in patients with established CV disease. It should be noted that while much of the discussion of polypills has focused on preventing an initial cardiovascular (CV) adverse event (primary prevention) in regions of the world with significant healthcare resource constraints, this advisory committee is not being asked to opine on this use. Also, this advisory committee is not being asked about the desirability of approving any particular polypill but rather a more general question regarding the kinds of information that FDA should request prior to deciding whether or not to approve a polypill for use in the United States. The committee is also not being asked to discuss the merit of any particular polypill development program to date, rather what evidence the committee would recommend be required for a de novo development program.

2. REGULATORY BACKGROUND

The Agency has approved many two- and a few three-drug antihypertensive fixed-combination drugs for use as first line therapy based solely on the demonstration that each component drug contributes to the effect on blood pressure (BP) {i.e., "(A + B) > A or B" rule[4]}. The Agency initially required sponsors of combination anti-hypertensive drugs to develop, and the Agency subsequently approved, all of the reasonable dose combinations, seeking to prevent the combination drug product from inhibiting titration of each component drug that could be titrated. It should be noted, however, that the Agency could not require the NDA holder to market all approved dose combinations, and some doses approved were subsequently withdrawn from the market. Over the last decade, the Agency has actively discouraged antihypertensive monotherapy and combination doses with effects that were very close together, considering them a nuisance, delaying patients achieving their blood pressure goal.

The Agency has also approved two fixed-combination CV drugs whose components had different mechanisms of action, aspirin plus pravastatin and atorvastatin plus amlodipine, for "patients for whom treatment with both component drugs is appropriate." The approvals of these two fixed-combination CV drugs were based on demonstration that neither component drug interfered with the other, either pharmacokinetically or pharmacodynamically. No clinical trial was deemed necessary to establish that co-administration preserved the outcome benefits.

The proposal to market a fixed-combination drug composed of aspirin, a statin, and one or more anti-hypertensive drug, all of which have cardiovascular claims, can be viewed as an extension of the approval of aspirin plus pravastatin and atorvastatin plus amlodipine. If the component drugs do not interfere with the serum concentrations of each other nor the pharmacologically effects of each other, then it can be assumed the clinical benefits of each component are preserved in the fixed-combination drug. However, unlike aspirin plus pravastatin and atorvastatin plus amlodipine, polypills are not intended to be titrated. What has been proposed is inclusion of one or two doses of the component anti-hypertensive drugs and statins, not all of the possible dose combinations. One reason proffered for not including all possible doses is that titration requires repeated interaction with health care providers which may be not be feasible and the benefits of titrating is unclear.

Approval of a polypill for a substitution claim is possible solely on the basis of demonstration that no component drug interferes with the other, either pharmacokinetically or pharmacodynamically. Polypills approved on this basis would be indicated for use as appropriate for patients who have been titrated to the doses of each component drug contained in the polypill and so can be switched to a polypill for convenience.

However the claim to be discussed by this meeting of the CRDAC is more general, the use of a polypill as therapy for prevention of secondary CV events without antecedent titration of the component drugs, based solely on demonstration that no component drug interferes with the other, either pharmacokinetically or pharmacodynamically.

While optimal care may include titrating the dose of some of the proposed component drugs to treatment goal, titration requires regular, fruitful interaction with a learned intermediary. We believe there are patients in the USA for whom cardiovascular prevention therapy is appropriate but whom are unlikely to receive the follow-up necessary for titration, for reasons which include geography, finances, and patient

preference. While it is possible that an applicant could decide to market multiple doses of a polypill with various doses of the component drugs, what has been discussed in scientific literature and the topic of the committee's discussion are fixed-dose combinations, not intended to be titrated. We are asking then whether people who are not, for whatever reason, going to receive regular follow-up are better off on some reasonable doses of drugs for secondary prevention of cardiovascular disease, rather than none, even if they are not getting what is believed to be optimal care.

3. THE PROBLEM OF MEDICATION ADHERENCE

3.1 The issue of poor adherence by patients to multiple medications

It is estimated that ~50% of all patients discontinue their prescription medication within 1 year of initiation, and an additional 35% discontinue their treatment after 2 years[5], and that because of poor adherence, 30–50% of prescriptions fail to produce the desired therapeutic results in patients with chronic medical conditions. Although reducing pill burden intuitively seems likely to improve adherence and/or compliance to therapy, not much information is available to support this theory. In a retrospective cohort study evaluating 10,526 participants in a US-managed care plan, patients receiving two or more medications in addition to their BP- and lipid-lowering agents were up to 45% less likely to adhere to their therapy than those receiving no or one additional medication[6].

Similarly, a retrospective claims analysis using data from several managed-care organizations during 1999 – 2000 demonstrated that the percentage of patients adhering to concomitant BP- and lipid-lowering therapies was significantly less than the percentage of patients adhering to either BP- or lipid-lowering therapy alone [32.9 vs.54.7% (P , 0.005) and 42.0% (P , 0.005), respectively, after 9–10 months][7].

3.2 Importance of treatment adherence in *secondary prevention* of CV disease

The efficacy of CV drugs in secondary prevention can be limited by poor adherence to treatment. Poor treatment adherence correlates with the number of pills a patient needs to take daily[8]. In this regard, taking only one tablet each day could improve adherence.

Non-adherence to secondary prevention treatment translates into increased morbidity and mortality. In a series of 1,358 patients discharged from hospital after an acute coronary syndrome, adherence to a combination of evidence-based medical therapies was independently and strongly associated with reduced 6-month mortality.[9] Multivariable survival analysis of the effect of medication discontinuation on mortality after a myocardial infarction in a series of 1,521 patients[10] found that discontinuation of secondary prevention therapy was independently associated with increased 1-year mortality (hazard ratio 3.81, 95% CI 1.88–7.72). In another study[11], adherence to statins and β-blockers correlated positively with survival, but this effect was not demonstrated with calcium-channel blockers, which is a drug class that has no definitive proven survival advantages in patients who have suffered a myocardial infarction. In a French registry that included 2,119 patients who had suffered a myocardial infarction, 1-year survival was 97% in patients who received aspirin, β-blockers and statins, compared with 88% in those who received none, one or two of these medications.[12]

Thus, the underlying tenet of the Polypill – that combination therapy is better than monotherapy - may well be correct with regard to the secondary prevention of CV disease.

In the clinical trials of Polypill reviewed in section 4, only one (UMPIRE[13]) trial of the three trials which included a usual care treatment arm reported adherence data (defined as taking aspirin, statin and 2 or more BP lowering drugs for at least 4 days per week) at 15 month as 86% in the intervention arm

compared with 65% in the comparator group (RR= 1.33; 95% CI 1.26, 1.41). However, the discontinuation rate among individuals randomized to fixed-dose combination was 22%.

3.3 Medication Disutility

The expected gain in lifespan from initiating statin therapy for an individual is considered medication utility. *Medication disutility* (or patient inconvenience) is aversion to medication which can be quantified as the gain in lifespan required by each individual to offset the inconvenience of taking an idealized daily preventative tablet. A random sample of 360 members of the general public in London were asked by face-to-face interviews at public thoroughfares to imagine an idealized tablet that was available at negligible cost, with no need for prescription nor medical supervision nor follow up blood tests, and to assume that the tablet would have no side effects and could be started or stopped at will with no consequence[14]. Disutility was assessed by asking subjects whether gaining an additional day of expected life would be sufficient benefit for them to commence lifelong therapy, and if the answer was negative, the subjects were asked if an additional 10 years of expected life would suffice. If the answer was positive, medication disutility was assumed to lie in the interval between 1 day and 10 years, and this range was progressively narrowed using a binary tree to reach the benefit required by each subject to offset their personal medication disutility. The researchers constructed tables (Paddington Life Expectancy Gain Charts) of expected gain in life span (utility) from initiating statin therapy for each age group, sex and CV risk profile in the population.

The observed median medication disutility was 6 months (inter-quartile range 1 to 36 months) to make daily preventative therapy worthwhile. Average expected longevity benefit from statins (utility) at age ≥50 years ranges from 3.6 months (low-risk women) to 24.3 months (high-risk men). The difference between the 2 values (Utility minus Disutility) is the net benefit of tablet therapy. Because utility has a much narrower spectrum than disutility, for those with a high disutility, regardless of utility, statins are a net harm; for those with low disutility, regardless of utility, statins are a net benefit.

These findings suggest that medication disutility cannot be assumed to be zero, and that over a quarter of patients had disutility exceeding the group-average longevity gain from statins expected even for the highest-risk (i.e., highest-gain) group. Future primary prevention studies may need to explore medication disutility in the intended patient populations, because patients may differ more in disutility than in prospectively definable utility which provides only group-average estimates.

3.4 Patient populations in which the Polypill may be useful

The combinations of agents with different therapeutic targets, such as aspirin plus pravastatin and atorvastatin plus amlodipine are approved for patients for whom treatment with both component drugs is appropriate; the approvals these combinations were based on demonstration that neither component drug interfered with the other, either pharmacokinetically or pharmacodynamically. These two combinations are approved to concomitantly reduce multiple risk factors without increasing the pill burden or the risk of adverse effects, and have the potential to improve CV risk factor management, thereby reducing the incidence of CVD. Although these fixed-combination drugs carry CV outcomes claims, no study was sought to establish the preservation of the outcome benefits. Because CV risk

factors, such as hypertension and dyslipidemia, frequently co-exist and interact in a multiplicative, rather than additive, manner[15], many large-scale CV outcome trials, such as the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – Lipid-Lowering Arm[16] (ALLHAT-LLA, n = 10,355) and the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid- Lowering Arm (ASCOT-LLA, n = 10,305), have included both antihypertensive agents and statins and demonstrated their safety and efficacy. Although some argue that additional studies are required to determine the optimal dose combination and the exact indications for each product, others believe that existing large-scale clinical trials are sufficient proof of safety and efficacy and that the development of combination pills should focus on drug delivery and packaging.

4. RANDOMIZED CONTROLLED CLINICAL TRIALS OF POLYPILLS

The following section includes a discussion of reports of clinical studies of various polypills. This review is being provided to further discussion of the kinds of evidence that might be needed to secure approval to market a polypill in the USA. It should be emphasized that these studies may not have been designed to serve as the principal support for an NDA. Further, the particular drugs studied may not have ever been intended to be developed for approval in the USA for secondary prevention of CV adverse events.

From MEDLINE and Google search of the medical literature published post-2000, I chose for review the following studies which are randomized, controlled, double-blind trials (RCTs) of a fixed combination of at least one anti-hypertensive drug and one statin versus a comparator (placebo, single drug or usual/standard care), and reported clinical outcomes.

Table 1 shows the compositions of different fixed combination polypills used in randomized, controlled trials reviewed in this Background document.

Table 1 Fixed dose combination drugs constituting the Polypill used in randomized clinical trials

Applicant or Clinical Trial	LDL-cholesterol lowering agent	Blood pressure lowering agent				Anti-platelet drug	Vitamin
	Statin drug	ACE-Inhibitor	Ca^{2+} channel blocker	Beta-blocker	Thiazide	Acetylsalicylic acid	Folic Acid
Polycap‡	Simvastatin	Ramipril	No	Atenolol	HCTZ	Aspirin	No
CUSP trial**	Atorvastatin	No	Amlodipine	No	No	No	No
Iranian trial	Atorvastatin	Enalapril	No	No	HCTZ	Aspirin	No
PILL trial§	Simvastatin	Lisinopril	No	No	HCTZ	Aspirin	No
TOGETHER trial	Atorvastatin	No	Amlodipine	No	No	No	No
CRUCIAL trial	Atorvastatin	No	Amlodipine	No	No	No	No
WHO study§	Simvastatin	Lisinopril	No	No	HCTZ	Aspirin	No
Wald & Law	Simvastatin	Losartan†	No	Yes	HCTZ	Aspirin	Yes
UMPIRE trial*	Simvastatin	Lisinopril	No	Atenolol	HCTZ	Aspirin	No
ASCOT-LLA∞ trial	Atorvastatin	Perindopril	Amlodipine	Yes	HCTZ	No	No
AVALON trial	Atorvastatin	No	Amlopidine	No	No	No	No
EUROPA trial	*Any lipid lowering*	Perindopril	No	No	No	Variable	No

*Either atenolol or HCTZ (hydrochlorothiazide) is added to Lisinopril; **used marketed drug Caduet; ‡Polycap is used in TIPS and TIPS-2 trials; †Angiotensin-Receptor Blocker; §used Red Heart Pill; ∞compared perindopril plus amlodipine to beta-blocker plus HCTZ

These short-term, randomized studies have evaluated various polypills containing from 1 to 3 antihypertensive agents and a statin and some contained aspirin. There were important differences among the studies in component drugs, patient populations enrolled (age, risk factors, region) and comparison treatment (placebo, active drug comparator or usual care). Generally they studied patients without CV disease at baseline. They were designed to determine the magnitude of change in BP or lipid levels and whether this magnitude was consistent with what would be expected based on trials of single agents; they were not powered to evaluate clinical outcomes.

When compared with placebo, the combination pills resulted in significant reductions in systolic and diastolic BP, and in total and LDL cholesterol. However, these reductions were sometimes less than what would have been expected from the component medications based on trials of these agents taken as single medications.

With regard to adherence, only one trial (UMPIRE[13]) of the three trials which included a usual care treatment arm reported adherence data (defined as taking aspirin, statin and 2 or more BP lowering drugs for at least 4 days per week) at 15 month as 86% in the intervention arm compared with 65% in the comparator group (RR= 1.33; 95% CI 1.26, 1.41). However, the discontinuation rate among individuals randomized to fixed-dose combination was 22%.

Review of individual studies follows.

4.1 TIPS

The Indian Polycap Study (TIPS)[17] was a double-blind trial in 50 centers in India, which enrolled 2,053 individuals without CV disease, aged 45–80 years, and with one risk factor, to determine the effect of the Polycap on BP, lipids, heart rate and urinary thromboxane B_2, and tolerability of the Polycap.

Subjects were randomly assigned to the Polycap (n=412) or to eight other groups, each with about 200 individuals, of aspirin alone, simvastatin alone, hydrochlorothiazide alone, three combinations of the two BP-lowering drugs, three BP-lowering drugs alone, or three BP-lowering drugs plus aspirin.

The primary outcome variables were LDL for the effect of lipids, BP for antihypertensive drugs, heart rate for the effects of atenolol, urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin, and rates of discontinuation of drugs for safety. Analysis was by intention to treat.

Compared with groups not receiving BP-lowering drugs, the Polycap reduced systolic BP (SBP) by 7·4 mm Hg (95% CI 6·1–8·1) and diastolic BP (DBP) by 5·6 mm Hg (4·7–6·4). Reductions in BP increased with the number of drugs used (2·2/1·3 mm Hg with one drug, 4·7/3·6 mm Hg with two drugs, and 6·3/4·5 mm Hg with three drugs).

Polycap reduced LDL cholesterol (LDL-C) by 0·70 mmol/L (95% CI 0·62–0·78), which was less than that with simvastatin alone (0·83 mmol/L, 0·72–0·93; p=0·04); both reductions were greater than for groups without simvastatin (p<0·0001).

The reductions in heart rate with Polycap and other groups using atenolol were similar (7·0 beats per min), and both were significantly greater than that in groups without atenolol (p<0·0001).

The reductions in 11-dehydrothromboxane B_2 were similar with the Polycap (283·1 ng/mmol creatinine, 95% CI 229·1–337·0) compared with the three BP-lowering drugs plus aspirin (350·0 ng/mmol creatinine, 294·6–404·0), and aspirin alone (348·8 ng/mmol creatinine, 277·6–419·9) compared with groups without aspirin.

The rate of noncompliance in the various treatment arms was about 15% over the 3-month follow-up period, of which about 4% was due to side effects.

Based on these results, the researchers projected that widespread and sustained use of the Polycap could reduce the risk of coronary heart disease (CHD) by 62% and stroke by 48%.

Reviewer's comments: It is not certainly known whether the data observed in the population in India would be similar in other regions and other ethnic groups.

The effect of Polycap on LDL-C was less than that with simvastatin alone, that on 11-dehydro-thromboxane B_2 was less than that of aspirin alone, and that on BP was less than that with two or three BP-lowering agents used. Thus, the effect of Polycap appears to be less than the combined effects of the individual components. The reasons are unknown, but could be due to baseline differences, low doses used (e.g., simvastatin at only 20 mg/d), drug interactions or non-adherence to the Polycap.

There was also an attrition bias in that follow up BP or heart rate were not obtained in 4% of participants, and follow-up lipids were unavailable in 9%. Individuals who were non-adherent to the Polycap and those who dropped out and were lost to follow up probably represent those who perceived no benefit of taking Polycap because they knew that they had normal CV risk levels.

4.2 TIPS-2

These researchers also conducted the Second Indian Polycap Study (TIPS-2)[18] in 518 individuals with previous vascular disease or diabetes mellitus from 27 centers in India to determine the incremental effects of 2 (full dose) plus potassium (K^+) supplementation versus single Polycap (low dose) on risk factors and tolerability.

After two 10-day run-in periods (during which subjects received low dose Polycap in the first 10-day period and full dose Polycap in the second 10-day period), subjects were randomly assigned to a single-dose Polycap or to 2 capsules of the Polycap plus K^+ supplementation for 8 weeks. The effects on BP, heart rate (HR), serum lipids, serum and urinary K^+, and tolerability were assessed using an intention-to-treat analysis.

The full-dose Polycap (plus K^+ supplementation) reduced BP by a further 2.8 mm Hg systolic (P=0.003) and 1.7 mm Hg diastolic (P=0.001), compared with that observed with the low-dose Polycap; there were no differences in HR (0.1 bpm).

The differences in total and LDL-C between full-dose and low-dose Polycap was 7.2 mg/dL (P=0.014) and 6.6 mg/dL (P=0.006), respectively, but there were no differences in high-density lipoprotein cholesterol or triglycerides.

The rates of discontinuation of the study drug after randomization were similar in the 2 groups (6.9% low dose versus 7.8% full dose).

The researchers projected that the full-dose Polycap (plus K^+ supplementation) reduces BP and LDL-C to a greater extent compared with the low dose Polycap (i.e., could reduce the risk of CHD by 69% and stroke by 57%), with similar tolerability.

Reviewer's comments: The TIPS-2 patient population had a previous CHD, which is an exclusion

criterion in the first TIPS trial. Therefore, the results of TIPS-2 trial cannot be compared to that in TIPS.

The TIPS-2 study has a potential bias in that due to a programming error, all participants randomized to the full-dose Polycap also received K^+, whereas none in the low-dose Polycap group received K^+. The authors maintain that this error was discovered only at the end of the study, and that all investigators at the sites or the coordinating centers were unaware of this during the conduct of the study, thereby maintaining the study blind (i.e., the Polycap dose comparisons were placebo controlled and double blind, whereas the K^+ supplementation was open) and that investigators ascribed adverse events to each component separately based on their judgment.

The researchers used two 10-day run-in periods to minimize early drop outs. During this run-in period 28.6% of patients discontinued participation. This could have a confounding effect on analyses.

Neither TIPS nor TIPS-2 study is powered to detect important differences in major adverse CV events.

4.3 CUSP trial

The Caduet in Untreated Subjects Population (CUSP) trial[19] was an 8-week, randomized, double-blind, placebo-controlled trial evaluating the efficacy/safety of the combination of a calcium channel blocker (amlodipine besylate) and a statin (atorvastatin calcium) in a single-pill form (5/20 mg) plus therapeutic lifestyle changes (TLC) compared with placebo plus TLC in 130 patients with comorbid hypertension (SBP=140-169; DBP=90-105 mmHg) and dyslipidemia (LDL-C= 110-160 mg/dl) without evidence of CV disease. At week 4, additional antihypertensive/lipid-lowering medication was permitted.

The primary end point was the proportion of patients in whom the dual goal of BP (<140/90 mm Hg) and LDL-C control (<100 mg/dL) was met at week 4. This dual goal attainment was significantly greater with amlodipine/atorvastatin plus TLC compared with placebo plus TLC at week 4 (47.6% vs 1.7%; P<.001), with further improvements at week 8. Most adverse events were mild to moderate.

The researchers concluded that therapy with single-pill amlodipine/atorvastatin plus TLC in these patients significantly increased dual BP/LDL-C goal attainment compared with placebo plus TLC.

Reviewer's comments: The CUSP trial supports the results of the GEMINI trial[20] (US-based with a largely white population): the dual BP/LDL-C goal attainment in the CUSP trial is comparable to that reported in GEMINI trial (55.6% in CUSP vs 57.7% in GEMINI at end point). However, CUSP is a small clinical trial (only 130 patients were randomized) of which 13 patients (7 in active arm and 6 in placebo arm) discontinued, and it is not known how the data from these discontinued patients were handled.

4.4 Pilot Polypill trial in Iran

The Iranian trial[21] was a double-blind randomized placebo-controlled trial in residents of Kalaleh, Golestan, Iran. Following an 8-week placebo run-in period, 475 participants, aged 50 to 79 years, without CV disease, hypertension or hyperlipidemia were randomized to fixed-dose combination therapy with aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg and hydrochlorothiazide 12.5 mg (Polypill) or placebo for a period of 12 months. The primary outcome variables were changes in LDL-cholesterol, systolic and

diastolic BP and adverse reactions. Analysis was by intention-to-treat basis.

At baseline, there were differences in SBP (6 mmHg). Taking account of baseline differences, at 12 months, Polypill was associated with statistically significant reductions in BP (4.5/1.6 mmHg) and LDL-C (0.46 mmol/l). The study drug was well tolerated, but resulted in the modest reductions in BP and lipid levels. In this study, the effects of the Polypill on BP and lipid levels were less than anticipated, which the investigators attributed to a lack of reliability of the reported compliance.

Reviewer's comments: This is a small clinical trial (475 randomized: 241 to Polypill, 234 to placebo) to test the effectiveness of a Polypill for primary prevention (i.e., in individuals without previous risk factors).

There were differences in BP and gender at baseline suggesting probable deficiencies in the randomization process.

There were more patients who discontinued the Polypill (8 patients) than placebo (4 patients) although only very few adverse effects were reported. There was a high rate of loss to follow-up at 12 months (32% in intervention arm and 22% in control arm).

The authors' own comparison of the treatment effect observed in this study with that in other studies show that there was a very modest reduction in CV risk (RR of 0.66 for CHD, and 0.798 for CVA), with an overall RR for CVD of 0.69, which is much less than that reported in TIPS, a similar population for primary prevention. The ACE inhibitor, enalapril that was used in this study may not have the CV risk protection demonstrated by ramipril (HOPE trial)[22] or perindopril (EUROPA trial)[23].

4.5 The PILL trial

The Program to Improve Life and Longevity (Pill) trial[24] was a randomized, double-blind placebo-controlled trial of a polypill (Red Heart Pill containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) conducted in 7 countries (Australia, Brazil, India, Netherlands, New Zealand, United Kingdom, and Unites States).

The study randomized 378 individuals without an indication for any component of the polypill, but who had an estimated 5-year Framingham CHD risk ≥7.5%, or if Framingham risk was between 5% and 7.5%, two or more additional untreated risk factors were needed (BMI >30 kg/m^2, waist circumference >102 cm in men or >88 cm in women, heart rate >80 bpm; fasting glucose 5.6-7 mmol/L, triglycerides >1.7 mmol/L, family history of first degree relative with premature ischemic heart disease or stroke (men <55 years, women <65 years) or GFR <60ml/min). The primary outcome variables were change in SBP, LDL-cholesterol and tolerability (proportion discontinued from randomized therapy) at 12 weeks follow-up. At baseline, mean BP was 134/81 mmHg and mean LDL-cholesterol was 3.7 mmol/L.

Over 12 weeks, Polypill treatment reduced SBP by 9.9 (95% CI: 7.7 to 12.1) mmHg and LDL-cholesterol by 0.8 (95% CI 0.6 to 0.9) mmol/L.

The discontinuation rates in the polypill group compared to placebo were 23% vs 18% (RR 1.33, 95% CI 0.89 to 2.00, p = 0.2).

There was an excess of side effects known to the component medicines (58% vs 42%, p = 0.001), which was mostly apparent within a few weeks, and usually did not warrant discontinuation.

The Red Heart Pill achieved sizeable reductions in SBP and LDL-cholesterol but caused side effects in about 1 in 6 people. The halving in predicted CV risk is moderately lower than previous estimates and the side effect rate is moderately higher.

Reviewer's comments: The study has a very short duration (12 weeks) of follow-up. Participants had high CV risk. However, the risk factor reductions in the PILL trial were roughly comparable to the TIPS trial in which Indian subjects without CV disease and only 1 or more CV risk factors were treated for the same duration (12 weeks).

The observed incidence of side effects in the PILL trial was greater than that predicted by Wald and Law, and the estimated reductions in risk of CHD and stroke in the PILL trial is about 25% - 30% less than that predicted by Wald and Law.

4.6 TOGETHER Trial

Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial (TOGETHER Trial)[25] was a 6-week, randomized, double-blind, double-dummy trial using hypertensive participants with additional CV risk factors without CVD/diabetes.

A total of 245 participants were randomized to either amlodipine/atorvastatin 5 to 10/20 mg + therapeutic lifestyle changes (TLC) (n=122) or amlodipine 5 to 10 mg +TLC (n=122); one participant did not receive any study medication.

The primary end point was the difference in proportion of participants attaining both BP (<140/90 mm Hg) and low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL) goals at week 6.

At week 6, 67.8% of participants receiving AML/ATO + TLC attained the combined BP/LDL-C goal versus 9.6% with AML + TLC (RD [A-B]: 58.2; 95% CI [48.1 to 68.4] P < 0.001; OR: 19.0; 95% CI 9.1 to 39.6; P < 0.001). Significant reductions from baseline in LDL-C, total cholesterol and triglycerides and estimated 10-year Framingham risk were also observed.

Treatment with AML/ATO was well tolerated. The researchers concluded that a multifactorial CV management approach is more effective in achieving combined BP/LDL-C targets as well as CV risk reduction compared with BP intervention only in this patient population.

Reviewer's comments: In this small population of 244 participants, the driving factor behind the significant results was the population LDL-C, and not the population BP probably because the participants were hypertensive patients many of whom were receiving amlodipine prior to the trial so that many patients in the AML+TLC arm were not receiving new anti-hypertensive medication; the trial, in fact, becomes one of atorvastatin vs placebo in hypertensive patients treated with amlodipine. This treatment effect was also observed in the CUSP trial (section 2.3, above) in which the LDL-C goal attainment far exceeds the BP goal attainment.

4.7 Randomized Polypill Crossover Trial in People ≥50 years of age

This randomized double-blind placebo-controlled crossover trial of a Polypill[26] was conducted among 86 individuals aged 50+ without a history of CV disease to compare the reductions in BP and cholesterol levels with those predicted from published estimates of the effects of the individual drugs. Participants were limited to residents of London or within easy travel to London.

Participants took the Polypill (amlodipine 2.5 mg, losartan 25 mg, HCTZ 12.5 mg and simvastatin 40 mg) each evening for 12 weeks and a placebo each evening for 12 weeks in random sequence.

The mean within-person differences in BP and LDL-C at the end of each 12 week period were determined. 84 out of 86 participants completed both treatment periods. Two patients discontinued during the first placebo period.

The mean systolic BP was reduced by 17.9 mmHg (95% CI, 15.7–20.1) on the Polypill, diastolic BP by 9.8 mmHg (8.1–11.5), and LDL-C by 1.4 mmol/L (1.2–1.6), which reflected reductions of 12%, 11%, and 39%, respectively. The results were almost identical to those predicted by the researchers; 18.4 mmHg, 9.7 mmHg, and 1.4 mmol/L respectively.

The researchers concluded that the Polypill resulted in the predicted reductions in BP and LDL-C, and suggested that long term reductions of this magnitude would have a substantial effect in preventing heart attacks and strokes.

Reviewer's comments: This is a small crossover study of 86 patients (84 completers). The concern for carryover effect is real, but the investigators considered that 12 weeks on the placebo was judged sufficient time for the drugs in the Polypill arm to have 'washed out.' This study is not designed to ensure that patients in the first part of the crossover trial return to baseline. There is a theoretical problem of a 'regression to the mean.' Also, the potential for carryover of adverse events that occur later in treatment periods is not possible to be ascertained.

4.8 CRUCIAL trial

Cluster Randomized Usual Care vs. Caduet Investigation Assessing Long-term-risk (CRUCIAL) trial[27] was a 12-month, international, multicenter, prospective, open-label, parallel design, cluster-randomized trial conducted in 19 countries in 4 geographical regions including Asia, the Middle East, Europe and Latin America, between March 2007 and October 2009.

This trial investigated whether a proactive intervention strategy based on single-pill amlodipine besylate/atorvastatin calcium (SPAA) in addition to usual care (UC) provided benefits on estimated CV risk, BP, and lipids (greater reduction in calculated Framingham 10-year CHD risk) compared to continued UC alone.

1,461 patients aged 35–79 years with hypertension (untreated or treated), total cholesterol (TC) ≤6.5 mmol/L (untreated), and three or more additional CV risk factors, with or without diabetes but without CHD, were enrolled at 136 sites (as clusters for cluster randomization) and received treatment. Patients randomized to the proactive intervention strategy arm were treated with SPAA at 5/10 mg to 10/10 mg

and, if approved in the participating country, this was increased to 5/20 mg and 10/20 mg. In the UC arm, patients were treated with the investigator's choice of any locally approved (and not contraindicated) antihypertensive and/or lipid-lowering drugs based on the investigators' clinical judgment, including, but not limited to, amlodipine, atorvastatin, or SPAA.

The primary efficacy endpoint was the calculated 10-year risk of developing CHD at 52 weeks using a Framingham CHD model. Secondary efficacy endpoints included post-baseline changes in BP and lipids, BP and LDL-C goal attainment, and additional measures of CHD or CVD risk such as the European SCORE 10-year risk of CV mortality[28], the 10-year Framingham risk for fatal and non-fatal CVD[29], and the Framingham stroke risk[30].

Mean baseline age and low-density lipoprotein cholesterol (LDL-C) were comparable between treatment arms. Mean baseline BP (150.3/89.7 vs. 144.3/86.5 mmHg) and Framingham CHD risk (20.0 vs. 18.1%) were higher in the proactive intervention versus the UC arm ($p < 0.002$ for both).

At week 52, mean absolute Framingham CHD risk was 12.5% in the proactive intervention arm and 16.3% in the UC arm ($p < 0.001$), which represented a relative risk reduction of -33.0% vs -4.0%. The difference, observed at weeks 16 and 52, was primarily driven by significant differences in systolic BP and in TC between the two arms.

Overall, adverse events AEs were reported in 48.8% and 44.0% of patients in the proactive intervention and the UC arm, respectively. The AE profile in the proactive intervention arm was consistent with previous safety experience for this medication.

Reviewer's comments: This is an open trial, so bias could be present in patients, personnel and primary outcome assessment. Randomization was by cluster randomization; each investigator serves "as a unit of randomization" which could introduce selection bias. Different doses of the intervention were available to investigators. There was a high rate of attrition (11.9% discontinued in the intervention arm and 6.5% discontinued in the usual care arm). How these patients' data were treated is not known.

4.9 WHO feasibility study for primary prevention of CV disease

This World Health Organization (WHO) feasibility study[31] was a pilot, open-label, parallel-group, randomized clinical trial involving three sites in Sri Lanka. A total of 216 patients without established CVD were enrolled. Patients had an estimated 10-year total CVD risk score >20%. The trial compared a Polypill (Red Heart Pill containing 75 mg aspirin, 20 mg simvastatin, 10 mg lisinopril and 12.5 mg HCTZ) to Standard Practice. Patients were recruited in a six-month period. After randomization, they were followed monthly for three months.

The primary outcome variables included reduction in SBP, total cholesterol and estimated 10-year CVD risk. The researchers also evaluated the recruitment process and acceptability of the Polypill by both physicians and patients. Two hundred three patients (94.0%) completed the treatment program and returned for their three-month follow-up visits.

There was no significant difference between the two intervention groups with regard to reduction in estimated 10-year CVD risk, SBP and Total cholesterol.

No safety concerns were reported. The majority of patients (90%) completed the trial; the researchers deduced that patients would take the Polypill "for life" if proven to be effective in reducing CVD risk.

About 86% of the physicians surveyed agreed with and supported use of the Polypill for primary prevention, and 93% for secondary prevention of CVD. Both the Polypill and Standard Practice resulted in marked reductions in systolic BP total cholesterol and 10-year risk of CVD. However, the differences between the treatment groups were not statistically significant.

Reviewer's comments: In contrast to TIPS, there was no difference between the Polypill and Standard Practice groups in terms of reduction in SBP, total cholesterol or 10-year risk of CVD. One problem revealed during data analysis was that the Standard Practice group received an unusually high level of care after randomization thereby raising this group's level of risk factor intervention (possible Hawthorne effect)[32,33]. The large changes in BP between baseline and follow-up visits may be due to poor standardization of the BP measurements.

While the researchers documented high acceptability of the Polypill to patients and physicians, they were unable to estimate the risk factor reductions on the Polypill because the control group received similar treatment with individual drugs.

4.10 UMPIRE trial

The Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial[Error! Bookmark not defined.] was a randomized, open-label, blinded-end-point trial among 2,004 participants with established CVD or at risk of CVD enrolled July 2010–July 2011 in India and Europe (England, Ireland and the Netherlands). The study objective was to assess whether FDC delivery of aspirin, statin, and 2 blood pressure–lowering agents vs usual care improves long-term adherence to indicated therapy and 2 major CVD risk factors, systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C).

Participants were randomly assigned (1:1) to an FDC-based strategy (n=1,002) containing either (1) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol, or (2) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide or to usual care (n=1,002). The trial follow-up concluded in July 2012.

The primary outcome parameters were adherence to medication (defined as self-reported use of antiplatelet, statin, and ≥2 BP-lowering medications) and changes in SBP and LDL-C from baseline.

At baseline, mean BP was 137/78 mmHg, LDL-C was 91.5mg/dL, and 1233 (61.5%) of 2004 participants reported use of antiplatelet, statin, and 2 or more BP-lowering medications. Median follow-up was 15 months (interquartile range, 12-18 months).

The FDC group had improved adherence vs. usual care (86%vs 65%; relative risk [RR] of being adherent, 1.33; 95%CI, 1.26-1.41; $P < 0.001$) with concurrent reductions in SBP (−2.6mmHg; 95%CI, −4.0 to −1.1mmHg; $P < 0.001$) and LDL-C (−4.2 mg/dL; 95%CI, −6.6 to −1.9 mg/dL; $P < .001$) at the end of the study. The changes in SBP and LDL-C over time and overall differences between treatment groups using a longitudinal generalized linear model shows that at the end of the study (median, 15 months), there was a 2.6 mm Hg difference ($P < 0.001$) in SBP (FDC − usual care) and a 4.2 mg/dL difference ($P < 0.001$) in low-density LDL-C (FDC − usual care).

The researchers reported that although there was consistency of effects across predefined subgroups, evidence existed of larger benefits in patients with lower adherence at baseline. In this subgroup of 727 participants (36%), adherence at the end of study was 77%vs 23% (RR, 3.35; 95%CI, 2.74-4.09; *P* <0.001 for interaction), SBP was reduced by 4.9mmHg (95% CI 7.3-2.6mmHg; *P* = 0.01 for interaction), and LDL-C was reduced by 6.7mg/dL (95%CI, 10.5-2.8mg/dL; *P* = 0.011 for interaction).

There were no significant differences in serious adverse events or CV events (50 [5%] in the FDC group and 35 [3.5%] in the usual care group; RR, 1.45; 95%CI, 0.94-2.24; *P*=0.09) between the groups.

The researchers concluded that among patients with or at high risk of CVD, use of an FDC strategy for BP, cholesterol, and platelet control vs. usual care resulted in significantly improved medication adherence at 15 months and statistically significant but small improvements in SBP and LDL-C.

Reviewer's comments: There are several limitations of the UMPIRE study design. Neither patients nor investigators were blinded to group assignment; this was not feasible.

The most important bias probably is that the intervention group patients were given the Polypill free of charge at study visits, whereas patients in the usual care group were required to pay for their medications as usual. Even though these patients generally had good medication adherence and a good understanding of how to obtain their medications, they were left to get them on their own, making it comparatively easier for the intervention group to obtain the medications. While cost was not a major issue in India and for older patients in Europe, it could have influenced adherence among the other patients because the Polypill was provided free. The researchers stated it was not possible to distribute the study medication through the normal distribution modalities; this could have affected adherence.

4.11 MESA Study

The Multi-Ethnic Study of Atherosclerosis (MESA) study[34,35] planned to investigate the association of smoking, weight maintenance, physical activity, and diet with coronary artery calcium (CAC), CV events, and mortality. This study is discussed here because it is tangentially related to the Polypill.

The MESA study recruited 6,814 participants 44 – 84 years of age and free from clinical CV disease at the time of enrollment at 6 academic centers in the US from 2000 to 2002. 585 subjects with missing lifestyle variable data were excluded. The final study population included 6,229 participants who were followed from 2000 to 2010. A lifestyle score ranging from 0 to 4 was created using diet, exercise, body mass index, and smoking status. CAC was measured at baseline and a mean of 3.1 (SD, 1.3) years later to assess calcium progression. The median time to last follow-up or death was 7.6 (SD, 1.5) years.

In another article, the researchers also used the MESA cohort to identify participants who met the inclusion criteria for 4 different Polypill distribution algorithms (TIPS, POLY-Iran, PILL trial and the original article by Wald et al), and then stratified them further based on CAC scores. The compared CVD event rates and the number needed to treat within each Polypill strategy stratified by CAC scores.

Over the follow-up period, 208 participants developed angina, 142 suffered a myocardial infarction, 20 experienced resuscitated cardiac arrest, 150 underwent percutaneous coronary intervention, 94 underwent coronary artery bypass grafting, and 41 died from CHD. Several participants suffered more than 1 CHD event; 305 unique participants suffered CHD events. A total of 374 participants died from

any cause over the course of the study: 41 from CHD, 15 from stroke, 1 from noncardiac atherosclerosis, 19 from other cardiac causes, 294 from noncardiac causes, and 4 from unknown causes.

Among MESA participants eligible for TIPS, Poly-Iran, Wald, and the PILL Collaboration, CAC = 0 was observed in 58.6%, 54.5%, 38.9%, and 40.8%, respectively. The rate of CHD events among those with CAC = 0 varied from 1.2 to 1.9 events per 1,000 person-years, those with CAC scores from 1 to 100 had event rates ranging from 4.1 to 5.5, and in those with CAC scores >100 the event rate ranged from 11.6 to 13.3. The estimated 5-year NNT to prevent 1 CVD event ranged from 81–130 for patients with CAC = 0, 38–54 for those with CAC scores 1 to 100, and 18–20 for those with CAC scores >100.

Participants with lifestyle scores of 1, 2, 3, and 4 were found to have mean adjusted annual calcium progressions that were 3.5 (95% confidence interval (CI): 0.0, 7.0), 4.2 (95% CI: 0.6, 7.9), 6.8 (95% CI: 2.0, 11.5), and 11.1 (95% CI: 2.2, 20.1) points per year slower, respectively, relative to the reference group (P = 0.003). Unadjusted hazard ratios for death by lifestyle score were as follows: for a score of 1, the hazard ratio was 0.79 (95% CI: 0.61, 1.03); for a score of 2, the hazard ratio was 0.61 (95% CI: 0.46, 0.81); for a score of 3, the hazard ratio was 0.49 (95% CI: 0.32, 0.75); and for a score of 4, the hazard ratio was 0.19 (95% CI: 0.05, 0.75) (P < 0.001 by log-rank test).

The researchers concluded that a combination of regular exercise, healthy diet, smoking avoidance, and weight maintenance was associated with lower coronary calcium incidence, slower calcium progression, and lower all-cause mortality over 7.6 years.

Reviewer's comments: In the MESA study, only 129 of 6,229 participants satisfied all 4 healthy lifestyle criteria, which may not have sufficient power to demonstrate differences in individual scores (especial those of score 4) in the CHD event analyses.

While lifestyle measures of diet, exercise, body mass index, and smoking status were evaluated, MESA did not measure cardiorespiratory fitness which may not be correlated with physical activity level because of co-morbid musculoskeletal conditions. Only smoking avoidance was associated with the greatest reduction in the risk of CHD and death. The study also identified CAC as a measure of subclinical vascular disease and biologic aging: MESA participants with a CAC=0 had very few CVD events whereas the majority of events occurred in those with a CAC>100.

The MESA study showed that among patients eligible for the Polypill treatment, the use of CAC screening could identify as many as 59% of the population with CAC=0 for whom the Polypill treatment is not necessary. The researchers suggested the use of CAC screening for the allocation of the Polypill.

5. RANDOMIZEDCLINICAL TRIALS OF COMBINATIONS OF ASPIRIN, LIPID-LOWERING AND ANTIHYPERTENSIVE DRUGS

5.1 ASCOT-LLA trial

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study[36], 19,342 hypertensive patients (aged 40-79 years) with at least three other CV risk factors were randomized to one of two antihypertensive regimens (amlodipine plus perindopril, or atenolol plus HCTZ). A sub-set of 10,305 patients with non-fasting total cholesterol concentrations ≤6.5 mmol/L was randomly assigned additional atorvastatin 10 mg or placebo: these patients form the lipid-lowering arm of the study. The planned follow-up was 5 years. The study was stopped after 3.3 years, at which time 100 primary events (combined endpoint of non-fatal MI including silent MI, and fatal CHD) had occurred in the atorvastatin group compared with 154 events in the placebo group [HR 0.64, 95% CI 0.50 – 0.83, p=0.0005].

5.2 AVALON trial

The Atorvastatin and Amlodipine in Patients with Elevated Lipids and Hypertension (AVALON) study[37] was a randomized, multicenter trial to assess the efficacy and safety of co-administered amlodipine and atorvastatin in patients with hypertension and dyslipidemia. 847 patients were randomized in an 8-week, double-blind, double-dummy, placebo-controlled period whereby patients received amlodipine 5 mg, atorvastatin 10 mg, amlodipine 5 mg plus atorvastatin 10 mg, or placebo. Thereafter, all patients received single-blind amlodipine 5 mg and atorvastatin 10 mg for 8-weeks, followed by 12 weeks of open-label treatment where doses could be titrated to improve LDL-C and BP control. At Week 8, 45% of the patients receiving amlodipine 5 mg and atorvastatin 10 mg reached both their BP and LDL-C goals, compared with 8.3% with amlodipine ($p < 0.001$), 28.6% with atorvastatin ($p < 0.001$), and 3.5% with placebo. At 28 weeks, 67.1% of patients co-administered amlodipine and atorvastatin achieved both targets. Framingham estimated 10-year risk of coronary heart disease declined from baseline levels of 15.1% to 6.9% at Week 28. Following co-administered treatment, the adverse events reported were similar to either agent alone.

The researchers concluded that concomitant administration of amlodipine and atorvastatin is an effective and well tolerated treatment for coexisting hypertension and dyslipidemia.

Reviewer's comments: In the two studies in which atorvastatin and amlodipine were administered as separate tablets, the effect size achieved by the combination was larger than that with each drug administered as monotherapy. In contrast, in the Polypill trials reviewed in Section 4, the reductions in BP and LDL-C by the combination in the Polypill were less than what would have been expected from each component of the combination when taken as monotherapy. It is possible that the short-duration of the Polypill trials may not have been adequate to portray the effect of the combination.

5.3 EUROPA study

In the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) study, a randomized, double-blind, placebo-controlled, multicenter trial to determine the efficacy of perindopril in reduction of CV events among 12,218 patients with stable CAD, 63% of patients in both the perindopril and placebo groups were found with hypercholesterolemia, and 57-58% of patients were on lipid lowering therapy. Treatment with perindopril reduced the relative risk for the composite primary efficacy endpoint event in all subgroups[38] regardless of whether they were receiving lipid-lowering agents or not. In a complementary Cox regression analysis to evaluate a possible interaction between treatment with lipid lowering agents and perindopril, the *p*-value for the interaction of perindopril and lipid-lowering agents was not statistically significant (p= 0.542) indicating that the relative risk reduction observed with perindopril was comparable between those who received lipid-lowering agents and those who did not.

This finding in EUROPA trial is different from the finding of the additive benefits of lowering LDL-C and BP in ASCOT-LLA and AVALON trials where amlodipine and atorvastatin were used.

Reviewer's comments: ACE inhibitors and statins have a common mechanism of action: they both reduce activation of the lectin-like oxidized LDL receptor and thus reduce oxidation of LDL cholesterol[39]. If the concentration of LDL cholesterol is sufficiently low, there is a theoretical possibility that ACE inhibitors – despite their activity in lowering BP – may no longer be effective in reducing the rate of CV events. The EUROPA and the PEACE trial[40] showed that in patients who were treated with a statin and had relatively low concentration of LDL cholesterol, ACE inhibitors were not able to reduce the rate of CV events.

6. SAFETY DATA FROM CLINICAL TRIALS OF POLYPILLS

The safety data are not clearly reported in the randomized trials of the Polypill presented in Section 3 of this Background Document. In a systematic review of Polypill studies by the Cochrane Collaboration, the Cochrane reviewers reported that "Adverse events were common in both patients who received Polypills (29.7%) and the comparator (24.2%) groups[41].

Patients who received Polypills were 20% (9% to 30%) more likely to report an adverse event, although none was serious.

Compared with those taking placebo, patients taking polypills were more likely to discontinue therapy (14% *v* 11%; 1.26, 1.02 to 1.55).

The potential risks of the Polypill are associated with 'hiding' active components in a single pill. If the name of the combination product does not reflect its active components, users may not be aware which drugs they are taking, will be less likely to inform their physician or pharmacist of their current medication(s) and are more likely to take additional agents that interact with their combination drug and lead to adverse effects. For example, the hidden inclusion of β-blockers in a combination product may be of concern for any patient with bronchospasm.

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